IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Cuttitta *et al.*
Application No. 10/571,012
Filed: March 8, 2006
Confirmation No. 4600
For: NON-PEPTIDE ANTAGONISTS OF GASTRIN RELEASING PEPTIDE
Examiner: Anna Pagonakis
Art Unit: 1628
Attorney Reference No. 4239-82094-06

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DECLARATION OF DR. FRANK CUTTITTA UNDER 37 C.F.R. § 1.132

I, Frank Cuttitta, Ph.D., declare as follows:

1. I am an inventor listed on U.S. Patent Application No. 10/571,012, filed March 8, 2006. I have read and am familiar with this application (hereinafter, "the subject application").

2. I hold a Ph.D. in Microbiology/Immunology from the University of Maryland. I am the Director of the NCI Angiogenesis Core Facility in Gaithersburg, Maryland. My *curriculum vitae* was made of record as part of the Declaration submitted with the Request for Continued Examination on September 10, 2010 (hereinafter "the September 2010 Declaration"). By virtue of my education, training, and professional experience, I am knowledgeable about the biology of cancer, angiogenesis, gastrin releasing peptide (GRP), and the identification and activity of agonists and antagonists of GRP function.

3. I have read the Office Action dated February 1, 2011 and the references cited therein.

4. I understand that the Office has rejected the claims of the subject application for allegedly being anticipated by Japanese Patent No. 10212235 (hereafter JP10212235) as evidenced by a slide from the National Cancer Institute (hereinafter, "the NCI slide").

Specifically, the Office asserts that "JP 10212235 clearly states that compounds of formula (I), including the elected compound, are useful for the treatment of tumors" (Office action, at page 5) and "though JP 10212235 is silent as to the effect of the elected compound to inhibit an activity of a gastrin releasing peptide (GRP), the administration of the claimed compound to patients suffering from cellular proliferative disorders *is expected to necessarily have the claimed effect* of inhibiting an activity of GRP, whether recognized by the author or not . . . . Further, the *treatment of a tumor would necessarily inhibit angiogenesis* since angiogenesis is responsible for the progression of the disease" (emphasis added, Office Action, at page 4). However, several features of the currently claimed invention distinguish it from JP10212235. Moreover, based on my training and experience, I do not agree that one of skill would *necessarily* reach the Office's conclusions regarding inhibition of GRP activity and angiogenesis.

5. Inhibiting GRP Activity Requires Expression of the GRP Receptor

5.1 The Office indicates that administration of a compound of generic formula (1) (hereinafter "Compound I") and its species to a subject as an "anti-tumor" therapy *necessarily* implies inhibition of a GRP activity. Based on my training and experience, I do not think that it is possible to support this inference without experimental evidence. First, the Office's assertion pre-supposes that *all* cancer treatments function through the same mechanism. As discussed herein (*see* ¶6.2), one of skill in the art would be well aware that different cancer treatments may or may not have the same cellular target. Second, the Office's assertion assumes that all cancers are mediated by GRP. This is not the case. Any cell (including a cancer cell) must express the GRP receptor to be sensitive to GRP. Without the GRP receptor, a cell cannot and will not respond to GRP in the cellular environment. Thus, without the GRP receptor in a given cell, a GRP-specific inhibitor cannot and will not inhibit an activity in that cell.

5.2 One example of a cancer cell type that is insensitive to GRP is leukemia, which is known not to express the GRP receptor. Additionally, it is well-appreciated that the GRP receptor is not even universally expressed in all cell lines of those cancer types known to express the GRP receptor. This concept is illustrated by Moody *et al.* (*J. Cell. Biochem. Supp.*, 24:247-256, 1996; submitted herewith as **Exhibit AA**). Lung cells are known to express the GRP

receptor. Moody *et al.* assay for the presence of the GRP receptor in several small cell lung cancer cell lines and several non-small cell lung cancer cell lines. Moody *et al.* demonstrate that the GRP receptor is present in many, but not all of the cell lines tested. Table I of Moody *et al.* shows that only 42% of small cell lung cancer and 32% of non-small cell cancer cell lines tested express the GRP receptor. Thus, the presence of the GRP receptor in a cancer type or cell line cannot be assumed without experimental verification or prior knowledge of its expression.

5.3 The claimed invention is directed to methods of inhibiting an aberrant GRP activity and methods of treating a condition that includes the step of "selecting a subject who is expressing GRP aberrantly or has an aberrant GRP activity." As discussed above, inhibiting a GRP activity requires that target cells express the GRP receptor. In contrast, JP10212235 does not require or suggest that the anti-tumor treatment based on Compound I inhibits an aberrant GRP activity. JP10212235 does not require that target cells express the GRP receptor. Nor does JP10212235 teach a step of selecting a subject who is expressing GRP aberrantly or has an aberrant GRP activity. JP10212235 describes an extensive list of cancer types that may be treated with Compound I and its species (¶35). However, this list includes cancer types, such as leukemia, that are known not to express the GRP receptor. Moreover, in view of Moody *et al.*, one of skill would have appreciated at the time of Applicants' priority date that even those cancer types known to express the GRP receptor will have derivative cell lines or disease strains that do not. Thus, without specifying that the treatment is inhibiting an aberrant GRP activity or indicating particular cell lines known to express the GRP receptor, JP10212235 does not *necessarily* describe inhibition of an aberrant GRP activity. Nor would one of skill infer that JP10212235 describes inhibition of an aberrant GRP activity.

6. Tumor Progression Requires Two Distinct Biological Processes

6.1 Tumor progression requires two distinct biological processes: (1) cell proliferation and (2) angiogenesis. Cell proliferation requires action of one or more factors on or in a *tumor cell* to induce cell division. Angiogenesis requires action of one or more factors on *endothelial cells* of preexisting blood vessels to induce formation of new blood vessels. To develop beyond a small, size-restricted colony, a tumor requires an adequate blood supply, and

must induce angiogenesis. This process, sometimes referred to as the "angiogenic switch," is reviewed in detail by Hanahan and Folkman (*Cell*, 86:353-364, 1996; submitted herewith as **Exhibit BB**).

6.2 However, even with an abundant blood supply, a tumor *will not expand* and the disease *will not progress* without tumor cell proliferation. Thus, an effective anti-tumor therapy might inhibit proliferation and not affect angiogenesis. Likewise, an effective anti-tumor therapy might target angiogenesis without affecting proliferation. It is possible that a given tumor treatment will inhibit *both* cell proliferation and angiogenesis, but one of skill would not and could not make this conclusion, or any conclusion about the target of a therapy, without explicit experimental evidence. It is common to classify anti-tumor treatments by their mode of function, including effects on proliferation and angiogenesis (*see* for example the table on page 118 of Butowski and Chang, *Cancer Control*, 12:116-124, 2005; submitted herewith as **Exhibit CC**). Thus, without data showing inhibition of angiogenesis (and there is no such data in the cited reference), I could not and would not conclude that the stated "anti-tumor effect" of JP10212235 necessarily inhibits angiogenesis. In contrast, the subject application clearly describes that the recited compound of formula XV' (referred to herein as Compound 77427) inhibits angiogenesis mediated growth of a solid tumor, and this anti-angiogenic effect is explicitly demonstrated. The anti-angiogenic properties of Compound 77427 are described extensively in the subject specification as discussed in the September 2010 Declaration (*see* ¶¶10-12).

6.3 The NCI slide does not change the above conclusion about what JP10212235 *necessarily* describes. The NCI slide provides a "birds-eye" schematic view of tumor-induced angiogenesis. The slide illustrates tumor-induced blood vessel formation by release of angiogenesis-stimulating factors into the surrounding normal tissue. The NCI slide only indicates that induction of angiogenesis results in a "tumor that can grow and spread." Implicit in this illustration is the requirement for *proliferation in addition to angiogenesis* for a tumor to grow and spread. Thus, the NCI slide does not indicate that any given anti-tumor treatment will *necessarily* inhibit angiogenesis.

7. JP10212235

7.1 JP10212235 describes compounds of generic Compound I as anti-tumor agents. JP10212235 also describes the synthesis and some chemical properties of 131 species of Compound I. As discussed above, describing a compound as an "anti-tumor" agent does not indicate any *necessary* particular biological activity to one of skill in the art. The biological properties of the agent must either be determined from experimental data, implied by particular methods of its use (*i.e.* monitoring efficacy through measurement of a particular property such as angiogenesis), or knowledge in the art of analogous compounds. JP10212235 describes an anti-proliferative activity of nine species of Compound I (discussed below), but JP10212235 does not describe any effect of any compound on angiogenesis, nor does JP10212235 suggest that Compound I or any of its species can inhibit angiogenesis. Additionally, JP10212235 does not describe any criteria for selecting patients for administration of Compound I and its species (*e.g.* patients aberrantly expressing GRP, having an aberrant GRP activity, or diagnosed with a cancer type known to express the GRP receptor). Nor does JP10212235 describe criteria for measuring or detecting *in vivo* efficacy of the described compounds other than increased animal survival. For example, JP10212235 does not describe measuring reduction in tumor-induced angiogenesis nor measuring reduction in tumor size.

7.2 JP10212235 supports its description of Compound I and its species having anti-tumor properties with two sets of experiments. The first (shown in Tables 27-31) presents the *in vitro* effect of nine species (Compound 14, 44, 45, 63, 64, 70, 71, 78, or 125) on *proliferation of 54 different cancer cell lines*. No effect on angiogenesis was tested or implied by these experiments. Tables 27-31 show that many of the listed species have anti-proliferative activity. But each table has at least one blank space where no data is reported for a given species (*see* for example Table 30, Compounds 44, 45, and 63). I conclude that these omissions indicate that no anti-proliferative effect was observed using the given species on the indicated cell line. More generally, these results demonstrate: (1) **considerable variability** among the biological effects of the tested compounds, and (2) the anti-proliferative effect of every species of Compound I **cannot be assumed** for every cancer type listed in JP10212235 or even every cell line tested; it must be experimentally determined.

7.3 These conclusions do not contradict my previous statements about the efficacy of Compound 77427 to treat a wide variety of GRP-related conditions (*see* the September 2010 Declaration, ¶14). As discussed therein, Compound 77427 was identified as a small molecule mimetic of the GRP functional antagonist monoclonal antibody 2A11. Thus, one of skill could reasonably predict that Compound 77247 will be useful to treat any disease or condition known to be mediated by aberrant GRP expression. In contrast, the biological target(s) of Compound I and its species is neither described nor suggested. JP10212235 does not suggest that Compound I and its species share a biological target (*e.g.* a particular protein). Thus, one of skill could not make the same inference about Compound I and its species that can be made about Compound 77427.

7.4 The second set of experiments described in JP10212235 (presented in Table 32) involves administration of Compound 44 to mice injected with *leukemia cell line* P388, and measurement of subsequent animal survival time. It is recognized in the art that leukemia does not form solid tumors. JP10212235 does not describe measuring any *in vivo* effect of administering Compound 44 other than increased subject survival time. JP10212235 does not describe *in vivo* measurement of cell proliferation, tumor size or angiogenesis. Nor is leukemia cell line P388 among the leukemia cell lines used in the *in vitro* assays (*see* Table 27, top section). No other compound was tested for *in vivo* effect. From this experiment, I conclude that Compound 44 has some anti-cancer effect, but without additional data, this effect cannot be defined. Additionally, because it is the only compound tested *in vivo*, and because the other experiment described in JP10212235 shows that species of Compound I have widely variable activities in the *in vitro* assay, it is not possible to infer any general properties of Compound I or its species from the *in vivo* data. Moreover, the GRP receptor has not been detected on leukemia cells. Thus, Compound 44's undefined anti-cancer effect cannot imply anything about any potential anti-GRP effect of Compound 44 or any other species of Compound I.

7.5 The Office equates Compound 105 and recited Compound 77427. Even though these compounds are the same, one of skill in the art could not infer any properties about Compound 105 from the *in vitro* or *in vivo* data presented in JP10212235. Compound 105 is not

used in any of the described experiments, nor does the data presented in JP10212235 describe or suggest any specific efficacy of Compound 105 that would motivate one of skill to test it. One of skill in the art could not infer anything about the biological effects of Compound 105 from the presented data because the chemical structure of Compound 105 is quite different from the nine tested compounds. To illustrate these differences, submitted herewith as **Exhibit DD** is a comparison of the structures of the nine compounds used in the experiments with that of Compound 105. **Exhibit DD** provides the structural description of the nine particular species that were tested in experiments in JP10212235 (copied from Tables 1-26), as well as Compound 105 (which was not tested). As shown in **Exhibit DD**, it is clear that all of the compounds used in the *in vitro* and *in vivo* experiments have a cyclic, branched functional group at the position labeled R3 that is distinctly different from the non-cyclic, unbranched R3 group of Compound 105. It is also clear that all nine of the tested compounds share very similar R3 groups. Because of these structural differences between the nine similar tested compounds and Compound 105, one of skill in the art would not have been able to necessarily infer that Compound 105 would share any biological property with any of the other compounds presented in **Exhibit DD**.

7.6 The September 2010 Declaration describes Compound 77427 as a small molecule mimetic of the GRP functional antagonist, monoclonal antibody 2A11 (*see* ¶8). Just as changes in an antibody's peptide structure may significantly affect its binding specificity, so too changes in chemical structure of a small molecule mimetic will affect its activity. As shown in **Exhibit DD**, the differences in structure between Compound 105 and the nine tested compounds are sufficiently significant that without experimental evidence, I do not believe one of skill would or could infer that Compound 105 shares the same biological properties as the other nine compounds.

8. In conclusion, based on my training and experience, I believe that the claimed invention is not described or suggested by JP10212235. Additionally, I do not believe that the data presented in JP10212235 would motivate one of skill to use Compound 77427 to inhibit an aberrant GRP activity such as angiogenesis mediated tumor growth.

9. I hereby declare that all statements made herein are of my own knowledge, are true and that all statements made on information and belief are believed to be true. Furthermore, these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4/28/11
Date

Name Frank Cuttitta, Ph.D.